‘A Sharp Intake of Breath’
Advances Across the Respiratory Space

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Defined Health
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  – FX125L Broad Spectrum Chemokine Inhibitor
  – Pan-Selectin antagonists
  – Overcoming Generic Singulair
  – LAMA’s for asthma?
  – LABA debate – implications for novel combinations
• COPD
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  – IL-8 focus of differing approaches
  – HI164OV H.flu vaccine
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  – VX770/VX809 CFTR modulation
  – Arikace/Aeroquin – inhaled antibiotics
• IPF
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• Bronchiectasis
  – Bronchitol – inhaled mannitol
• Conclusions

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Prevalence and Unmet Needs for Respiratory Indications in the US, EU5 and Japan

* Estimated global prevalence (7-market estimated are not available). All other estimated prevalence rates are for 7 major markets (US, EU5 and Japan).

Source: DH Insight
Epidemiology Drives The Majority of Market Sales
Orphan Indications Generate Significant Revenues

- The major markets of allergic rhinitis, asthma and COPD account for approximately 80% of the reported $42B in revenue for the entire Respiratory Market in 2009
- Significant revenue is generated in established orphan indications, most notably PAH and Cystic Fibrosis, with approved therapies adopted by the overwhelming majority of patients and commanding high prices

<table>
<thead>
<tr>
<th>Disease</th>
<th>7 Market Prevalence (US, EU5, JP)</th>
<th>2009 WW Pharma Sales**</th>
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<tr>
<td>Asthma</td>
<td>67M</td>
<td>$16B</td>
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<tr>
<td>COPD</td>
<td>41M</td>
<td>$10.5B</td>
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<tr>
<td>Allergic Rhinitis</td>
<td>154M</td>
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<tr>
<td>PAH</td>
<td>150K (global)</td>
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<tr>
<td>Cystic Fibrosis</td>
<td>80K (global)</td>
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<td>ARDS</td>
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<td>NRDS</td>
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<td>IPF</td>
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<tr>
<td>Scleroderma of the Lung</td>
<td>10.5K</td>
<td>N/A</td>
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</table>

** As reported in Evaluate Pharma and/or additional market research reports obtained by Defined Health. Sales reported in US dollars.
Respiratory Development in Context

Respiratory development in the top companies, as captured by Cowen, lags behind the major indications of Oncology and CNS, but still indicates the high level of unmet need across this therapeutic area.

<table>
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<tr>
<th>Therapeutic Category</th>
<th>PC</th>
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<th>II</th>
<th>III</th>
<th>NDA</th>
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<tr>
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<td>276</td>
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<tr>
<td>Average</td>
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<td>19</td>
<td>18</td>
<td>14</td>
<td>6</td>
<td>60</td>
<td>179</td>
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</tbody>
</table>

*Score: 5 points given to each product with NDA filed; 4 points to each in Phase III; 3 points to each in Phase II; 2 points to each in Phase I; and 1 point to each in preclinical development.
Allergic Rhinitis
The Global Prevalence of Allergic Rhinitis is High but Varies Between Countries

• Allergic rhinitis is considered to be the most prevalent immunologically-mediated disease in the world and thus affects a large number of people in both developed and emerging markets.
• The prevalence of allergic rhinitis varies within and among countries, largely due to geographic differences in the types and potency of different allergens and the overall allergen burden.
• Overall, it is thought that between 40-50% of all allergic rhinitis patients are diagnosed. In the US, it is estimated that there are between 8-20 million drug-treated patients.
• Recent figures suggest an approximately equivalent 20% prevalence rate for the US, Big 5 EU and Japan.

Unmet Needs in the Allergic Rhinitis - Limited to Chronic Non-responders and Patients with Severe Allergies

Well Managed

80-90%

Reflected to Allergist

Unmet Needs

Not Well -Managed

10-20%

Target Patient Population

Patients with Severe Allergies

Chronic Non-responders

Strength of Evidence for Efficacy of Treatment Modalities

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Intermittent</th>
<th>Persistent</th>
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<tbody>
<tr>
<td>Oral Antihistamines</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Intranasal Antihistamines</td>
<td>A</td>
<td>A</td>
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<tr>
<td>Intranasal Corticosteroids</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Intranasal Cromones</td>
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<td>A</td>
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<tr>
<td>LTRAs</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Subcutaneous SIT</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Sublingual SIT</td>
<td>A</td>
<td>B</td>
</tr>
</tbody>
</table>

A = provides substantial benefit; B = provides modest benefit

VTX-1463 a TLR8 Agonist for Allergic Rhinitis

- VentiRx’s TLR8 agonist - VTX-1463 is focused on seasonal and perennial Allergic Rhinitis (AR).
- TLR8 recognizes single strand RNA as its natural ligand. Genetic studies show link between TLR8 and asthma/AR.
- Results from two Phase Ib randomized double-blind studies (in/out of grass pollen season) using the Vienna Challenge Chamber, show significant improvement in nasal symptoms as measured by total nasal symptom scores and anterior rhinomanometry.
- VTX-1463 is delivered as a nasal spray on a Qweekly basis.
- Adverse events were generally mild, better with 100μg maximum dose than 250μg. Dose optimization and timing will be essential to commercial success.

- MOA for TLR’s not fully characterized – TLR8 stimulates production of IL-12, IL-10 in human monocytes and myeloid dendritic cells and provides early benefit through mast cell modulation and subsequent doses modulate local T-cell responses and decrease Th2 tone.
- TLR8 is able to recognize small synthetic molecules (MW<500Da) so is a good potential target for drug development.

Source: Horak, F Expert Opin Investig Drugs 2011; 20(7):981-986, Also presented at AAAAI March 2011
Asthma
The Global Prevalence of Asthma is Continuing to Rise

- Asthma is a serious global health problem, with an estimated 300 million individuals affected worldwide and the prevalence is continuing to grow.
- It is estimated that there will be an additional 100 million persons globally with asthma by 2025.
- Nonetheless, the prevalence of asthma varies widely by country, reported to occur from 1% to 18% of populations.
- in developed countries, it is estimated that approximately 75% of the asthma population has been diagnosed, with a remaining 25% remaining undiagnosed.
- Asthma accounts for approximately 500,000 hospitalizations per year and approximately 250,000 deaths per year are attributable to asthma.

Unmet Needs Exist for Distinct Subpopulations of Asthma Patients

• The vast majority (~85%) of asthmatics are satisfactorily controlled by regular use of available medications. However, there are subgroups of asthmatic patients that respond poorly or not at all to current therapies. Current unmet needs include:
  – **Efficacious therapies for severe patients** who have failed available interventions and must take oral prednisone.
    • A recent example of this is Xolair, which has achieved this position in the treatment algorithm despite failing to improve FEV₁ in clinical trials (decreased exacerbation frequency).
  – **An oral alternative to ICS** with the same efficacy.
    • Current drivers here are poor patient compliance and public perception that inhaled steroids are dangerous.
  – **Reversal of remodeling** in patients suffering long-term asthma would be highly valued.
    • These patients often have remodeling in their lungs leading to irreversible damage, similar in fashion to COPD patients.
  – **Treatment options for “Brittle Asthmatics”,** who are a small proportion of mild asthma patients.
    • In these patients, their symptoms are very easily controlled for long stretches of time, but tend to suffer extremely severe exacerbations requiring ICU care.

IL13/IL4 Only for a Subset of Patients?

- Failure of Amgens AMG317, Aerovance’s Aerovant and Altair’s Air645 highlights difficulty in developing medications for a broad asthma population, when (with hindsight) they are better focused on a limited patient segment.

- Redundancies of immune biology mean that highly targeted approaches thought to address the key pathways of asthma have been shown more often than not to fail.

- IL-4 has been perceived as having a central role in asthma as it was thought to be key for Th2 immune responses, in the absence of IL-4 signaling it was assumed that Th2 associated eosinophilic airway inflammation and IgE sensitization would not develop.

- However, it is now clear that there are a number of redundant pathways existing for Th2 deviation, involving IL-25, IL-33 and TSLP that limit the ability of IL-4 inhibition to fully control asthma. In addition IL-13 has twin pathways to IL-4 and is more widely expressed, making it an equally important factor in the asthma cascade.

The key question is whether the subsets of patients with eosinophilic asthma have complete overlap with those treated by Xolair or if these are distinct groups allowing exploitation of specific niches.

Source: DH Insight; Barnes PJ, Nature Reviews immunology vol 8, March 2008
FX125L (Funxional Therapeutics)

- Funxional Therapeutics has a novel oral small molecule Broad Spectrum Chemokine Inhibitors—somatotaxin—FX125L ready for Phase II studies in asthma.

- Series B venture funding of €10M was raised in May 2010 for Phase II development.

- A number of studies in a wide range of animal models suggest that FX125L may have similar efficacy but better safety than corticosteroids.

- Phase I study results linear PK, a half life of 25 hours and good tolerability profile.

  Jill Reckless, et al abstract 1418, EAACI 2009

  “...Broad spectrum chemokine inhibitors such as FX125L represent a promising new class of therapeutics for the treatment of allergic asthma, with the possibility of efficacy in neutrophil-dominated steroid-resistant asthma and COPD.”

Source: Funxional Therapeutics website

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Pan-Selectin Antagonists
Bimosiamose (Revotar Biopharmaceuticals)

• Bimosiamose is a small-molecule antagonist of E-, P- and L-selectins (pan-selectin antagonist) being developed by Revotar Biopharmaceuticals for the treatment of asthma, COPD, psoriasis, acute lung injury and adult respiratory distress syndrome (ARDS).
  – Selectins, along with other cell adhesion molecules such as integrins and members of the immunoglobulin superfamily, control leukocyte extravasation, migration within the interstitium, cellular activation, and tissue retention. Therefore, interfering with selectin activity may provide a means to prevent the accumulation of inflammatory cells.
  – Bimosiamose is a glycomimetic of sialyl Lewis X, a natural selectin-binding compound originated by Encysive (now a subsidiary of Pfizer) and has been licensed to Revotar Biopharmaceuticals.

• Summary of clinical trials for Bimosiamose:
  Asthma
  – Two Phase IIa trials of bimosiamose in patients with asthma have been completed. One trial investigated bimosiamose as an IV therapy and the other evaluated an inhaled formulation of bimosiamose. Revotar appears to be continuing development with the inhaled formulation.
  – Two Phase I studies of an inhaled formulation of bimosiamose were completed in 2001. Bimosiamose was well tolerated in each study and detectable plasma levels were achieved at higher dose levels.

  COPD
  – A Phase IIa ozone-induced airway inflammation study in 18 GOLD II/III COPD patients has been completed. Bimosiamose compared to placebo statistically reduced sputum neutrophils (40%), IL-8 (35%) and MMP9 (46%). A further placebo controlled Phase II study (60 GOLD II/III non-smoking patients) is ongoing.

Source: Kirsten A et.al. Pulm Pharmacol Ther 2011 Apr 14 Epub; Revotar AG website
Overcoming Generic Singulair

- The advent of generic Singulair in 2012 may herald the potential for greater use of ICS/LTRA combinations (2 generics) instead of moving to branded ICS/LABA combination products like Advair & Symbicort.

- Studies have shown that asthma patients with concomitant allergic rhinitis are at greater risk of asthma attacks and have more visits to ER. LTRA’s are known to work well in this large patient sub-population (Busse et al 2006, Philip et al 2004).

- A number of studies have demonstrated equivalence between ICS/LTRA and ICS/LABA combinations (e.g., IMPACT), although the Cochrane Review (2006) favored the ICS/LABA combination.

- Novel compounds CRTH2/PGD2 antagonists or FLAP inhibitors with the potential to replace ICS will need to be aware of the potential for a challenge from a generic based ‘steroid sparring’ regimen for uncontrolled mild/moderate asthma patients.

- Identification of sub-sets of patients will be key to prove efficacy of new agents and avoid direct comparison with combinations of generic products.

Source: Bjermo L Ther Adv Resp Dis 2008;2(3):149-161

Results from sub-analysis of the IMPACT study. Patients with concomitant rhinitis had a greater risk of having an asthma attack or being referred to the emergency room (ER) due to an asthma attack [Bousquet et al. 2005].

Results from the IMPACT trial comparing salmeterol 100 μg day versus montelukast 10 mg/day as add-on treatment to fluticasone 200 μg/day on the prevention of severe asthma exacerbations in patients with mild-moderate asthma. Both treatment arms provided excellent preventive effect without any differences between the groups. Adapted from Bjermo et al. [2003].
LAMA’s for Uncontrolled Asthma?

- An October 2010 paper in NEJM (supported by NHLBI) looked at the addition of a LAMA (tiotropium) for uncontrolled asthmatics on low dose ICS compared to doubling the dose of ICS or addition of LABA to the ICS regimen.
- Results indicate a potential use for LAMA as addition to low dose ICS for uncontrolled asthmatics. Addition of LAMA proved equivalent to addition of LABA and both statistically better than high dose ICS alone.
- Using the study’s two-dimensional criteria: Goal to treat the greatest number of patients with a drug to which they had a response and to maximize the use of inhaled glucocorticoids – 53.1% of patients would be treated with a double dose of an inhaled glucocorticoid, 8.8% with tiotropium plus an inhaled glucocorticoid, and 8.1% with salmeterol plus an inhaled glucocorticoid, leaving 20.6% to be treated with either one of the bronchodilators combined with a low-dose inhaled glucocorticoid and 9.4% who had no response to any treatment.
- Further investigation of LAMA’s could prove useful, especially in asthma patients that smoke (known to respond better to anti-cholinergics). This may avoid the LABA safety debate!

Shown are the mean differences among patients receiving tiotropium, those receiving double-glucocorticoid, and those receiving salmeterol with respect to the morning peak expiratory flow (PEF) (Panel A), the evening PEF (Panel B), the prebronchodilator forced expiratory volume in 1 second (FEV1) (Panel C), and the proportion of asthma-control days per 14-day period (Panel D). The I bars indicate 95% confidence intervals.

Source: Peters S et al NEJM 2010; 363:1715-26
LABA/LAMA Debates

• FDA have had an issue with the relative safety of LABA’s for some time.

• FDA have now requested additional large safety studies (~53,000 patients) covering adults (12 years+) and children (4-11 years) for LABA’s in combination with ICS to identify and quantify the risks versus use of an ICS alone. The data from these studies are expected in 2017.

• This has an implication on novel combination drugs, where each single agent needs to be approved prior to approval of the combination – e.g., indacaterol (Novartis) high dose was not recommended by the Respiratory Advisory committee in March 2011 and FDA has requested until July 2011 to review the dossier prior to deciding on approval. Indacaterol is already approved in 50 other countries.

• Pfizer/BI’s Spiriva Respimat device is also the subject of controversy, as the FDA has recently cited the increased deaths seen with the device as a reason to ‘hold fire’ on approval – is this the budesonide Turbohaler all over again?

• The difficulty for all companies is that FDA seems out of step with other agencies and there is the potential for different approaches being required for US versus rest of the world.

Source: Reuters
COPD
The Global Prevalence of COPD is Tremendous but Highly Variable Among Countries

- According to WHO, there are over 200 million patients with COPD in the world and in the next few years COPD is predicted to overtake tuberculosis and respiratory infections to become the leading cause of death and disability attributable to respiratory disease worldwide.
- By 2030, it is predicted that COPD will become the 4th leading cause of death worldwide.
- Variances in prevalence among different countries is due to many factors, including pollutant exposure, smoking rates and access to health care.
- Globally, it is thought that patients diagnosed with COPD represent <50% of the estimated prevalence rates.

Source: Global Initiative for Chronic Obstructive Lung Disease (www.GOLDcopd.com), Defined Health knowledgebase, World Health Organization.
Unmet Needs Exist for All COPD Patient Groups and Segments

- Available treatments for COPD are mainly palliative and there are no therapies available that halt the decline in lung function or the progressive destruction of the airways associated with COPD.
- As such, unmet needs exist across all facets of the disease:
  - **Unmet Needs of the COPD Patient**
    - More effective diagnosis and primary prevention
    - Better symptom control
    - Fewer exacerbations
    - Slowing of disease progression
    - Better life expectancy
    - Less systemic disease secondary to COPD and fewer co-morbidities
  - **Unmet Needs of the Medical Community**
    - Optimizing disease prevention
    - Improving symptom control
    - Preventing exacerbations and decreasing their clinical impact
    - Preventing disease progression
    - Reducing disease-related mortality
    - Identifying systemic effects and co-morbidities

Current Management - Devices

COPD is a multi-billion dollar market defined by pulmonary inhalation devices delivering agents that provide only symptomatic relief.

Source: DH Insight, Company websites
PDE-4 Inhibitors – Add-on or More?

- Roflumilast (Launched EU Nycomed and US Forest).
  - Balanced PDE-4 D & B inhibition. Good anti-inflammatory but weak bronchodilating effects compared to theophylline.
  - Oral, QD dosing, with/without food.
  - Indicated to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.
  - Two studies of a total of 1,537 moderate to severe COPD patients, demonstrated an improvement in exacerbation frequency versus placebo (15% and 18% reduction).
- A number of other PDE-4 products are in development for COPD: Tetomilast (Ph II/III, Otsuka); OX914 (Ph II, Orexo); MK0873 (Ph I, Merck); Ronomilast (phase I, Biotie)
- Time will tell as to whether the known AE’s will allow a wider spread utility for PDE-4’s.

Source: Calverly PMA et al, Am J Respir Crit Care Med 2007; Daliresp FDA labeling Feb 2011; ADIS R&D
IL8 - CXCR2, CXCR1 Antagonists, IL8 Decoy

• While IL8 has been the focus of many studies, other chemokine receptor ligands appear to be activated in COPD (CXCL1, CXCL5), and capable of modulating neutrophilic inflammation.
• Redundant signaling modalities may explain the disappointing failure of Abgenix’s anti-IL8 monoclonal antibody therapy in psoriasis and COPD.
• A few companies have now shifted their focus from ligand to the receptor. Merck, AstraZeneca and GSK all have CXCR2 inhibitors. Merck’s SCH 527123 was the most advanced but it is unclear how development is progressing.
• ProtAffin is using a different approach – a glycan binding decoy protein based on IL8. This modified wild-type IL8 binds to glycans at the cell surface level to inhibit the neutrophilic inflammation cascade from IL8/CXCR1/2 up-regulation.

Source: Ligand Pharmaceutical 8k Report (02/2009); ProtAffin company information; ADIS R&D
HI 164OV – Hunter Immunology

- COPD patients are routinely given annual S.pneumoniae and influenza vaccines to reduce risk of exacerbations. H.influenzae is known to play a role in both chest infections and reduction of ciliary clearance.
- The non-typeable Haemophilus influenzae (NTHi) therapeutic vaccine is an approach focused on reduction of the potential for respiratory pathogens to trigger exacerbations. Clinical studies have shown that NTHi is associated with 15-86% of COPD-related exacerbations, highlighting the clinical relevance of NTHi infection and targeted therapeutic vaccines.
  - In more recent studies, NTHi therapeutic vaccine was shown to reduce exacerbations (40%), antibiotic and corticosteroid use, and – most importantly- hospital admission (90%) relative to placebo.
  - NTHi is not covered by the current Haemophilus influenzae type b vaccine.
- New Phase IIb study is commencing in 340 COPD patients at 23 sites in Australia. Results expected March 2012.

Source: Hunter Immunology company information
Pearl – PT003

• Pearl Therapeutics have in development PT003 a BID combination of formoterol (LABA) and glycopyrrolate (LAMA) in a HFA MDI device.

• Recent Phase IIb data presented on PT003 are compelling as the combination worked better than the constituents and had a greater effect than tiotropium plus formoterol.

• The study’s primary endpoint was improvement in lung function after one week of dosing, as assessed by FEV1* AUC0-12 relative to baseline at the start of treatment. Treatment with PT003 resulted in a statistically significant improvement in mean FEV1 AUC0-12 of 47% (or 93 mL) over Foradil® and 49% (or 95 mL) over Spiriva® after one week of dosing (p<0.0001 for both comparisons).

• PT003 also demonstrated a statistically significant improvement in peak FEV1 on day one, with further benefit observed on day seven relative to all comparators and placebo. Treatment with PT003 yielded an improvement in peak FEV1 levels of 42% (or 64 mL) over Foradil® and 74% (or 92 mL) over Spiriva® as measured on day one; and an improvement of 37% (or 89 mL) over Foradil and 75% (or 141 mL) over Spiriva® when measured on day seven (p<0.03 for all comparisons).

• Furthermore, PT003 demonstrated a faster onset of action than Spiriva® on day one (75% higher probability of onset at any time point during the first 2 hours following administration, p≤0.0003).

• These results, if confirmed in Phase III studies, point the way to not only improving FEV1 the end-point for FDA, but also providing key benefits to COPD patients as they will be able to ‘feel’ the product working from the start of therapy, reinforcing patient compliance and a better overall outcome.

Source: Pearl therapeutics company information; DH insight
Cystic Fibrosis
The Pathophysiology of Cystic Fibrosis is Well Established

- The CF gene defect leads to an absent or malfunctioning CFTR protein, which results in abnormal chloride conductance of epithelial cells.
- In the lung this results in airway surface liquid depletion and subsequent ciliary collapse and decreased mucociliary transport.
- The consequence of this is a vicious circle of:
  - Phlegm retention
  - Persistent infection
  - Chronic inflammation
- Over 1,000 mutations in CFTR have been described, although the most common CFTR mutation, ΔF508, is thought to occur in ~60% of CF patients.
- For reasons not entirely understood, patients with less common CFTR mutations and milder forms of the disease have a greater life expectancy than the majority of the CF population that have the classic form of the disease.

Pathophysiology Cascade in Cystic Fibrosis

Cystic Fibrosis is a Very Rare Disease that Almost Exclusively Affect Caucasians

- Cystic fibrosis affects an estimated 70,000 – 80,000 patients worldwide, with almost half of the entire patient pool residing in the US.
- The incidence of CF in all Asian countries, including Japan, is extremely low and estimated to be ~1/100,000 live births.

Source: Cystic Fibrosis Foundation (www.cff.org), Story, S and Wald, G. Nature Reviews Drug Discovery. 7:555-556.
Vertex VX770/VX809 – Not Yet the ‘Dream Team’ for All CF Patients

• Vertex Pharmaceuticals has two CFTR programs currently in late stage development. Recently published Phase III STRIVE Study of VX-770 in patients with the G551D CF gene defect (~4% of CF population) showed significant relative mean improvement in lung function of ~17% from baseline compared to placebo and a significant mean absolute improvement from baseline in the VX770 treated patients of ~10.5% compared to placebo. There were significant improvements in all key secondary end points – exacerbation frequency, weight gain and sweat chloride.

• Vertex also have VX809, a CFTR corrector that aims to increase trafficking of CFTR to the cell surface. This is being studied (Phase II) in combination with VX-770 (aiming to improve function of CFTR proteins) in CF patients with dual ΔF508 mutations (48% of US CF patients have this dual mutation, 39% have one copy of ΔF508). The assumption was that the combination may be able to provide enough correction to regain a more normal cell physiology across the broad CF population. The interim Phase II results did not demonstrate the broad effect on reduction of sweat chloride that some analysts had hoped. However in a sub-population (>VX770 responder population alone) there was an enhanced reduction in sweat chloride, although not as great an effect as that seen in the G551D STRIVE patients.

• It is not clear which patients will derive the most benefit from these (and the PTC) compounds. It is possible those with long established disease will still require their Pulmozyme and TOBI.

Source: Cystic Fibrosis Foundation; Vertex Press Releases
Arikace - Insumed / Aeroquin - Mpex

- Inhaled antibiotics in CF are established maintenance therapy thanks to TOBI. Draw back of adverse events (deafness) with extended usage and encouragement of resistant organisms.
- Aminoglycosides, fluoroquinolones and monobactams used/in development for reduction of *Pseudomonas* bacterial load.
- Insmed (Transave) announced positive Phase II data in June 2011 for Arikace (liposomal amikacin).
- Trial consisted of 6 cycles of Arikace - 28 days on, 56 days off.
- Arikace produced 5.7% relative improvement in FEV1 at end of 72 weeks. Mean 11.7% improvement in FEV1 from baseline at end of 28 day period of 6th cycle. Improvement in lung function in all cycles.
- Adverse events were consistent with expectations in CF patients receiving inhaled therapies. No increase in Pseudomonas MIC<sub>90</sub> observed after 6 cycles.
- Note: IV amikacin less nephro/ototoxic than IV tobramycin.
- Reduced time on medication is a real plus for CF patients. US composition of matter patent to 2026 a benefit for partners!
- **Benefit versus TIP (a DPI TOBI)** – reduced time on medication over a year. QD vs. BID when on treatment. Handheld nebulizer easy to use, but 13 mins admin time (560mg) vs. 4 mins (x2) for TIP.
- Mpex’s Aeroquin (240mg inhaled levofloxacin) also uses Pari nebulizer technology for 5 minute administration time/dose.
- Phase III study initiated early 2011- Aeroquin 240mg BID for 28 days, 28 days off.

Source: Insumed and Mpex company information
Idiopathic Pulmonary Fibrosis
The Epidemiology of IPF is Not Well Understood and Prevalence Rates are Highly Variable Among Countries

- IPF has no distinct geographical distribution and has been reported in both rural and urban settings with no predilection by race or ethnicity.
- In the US, the reported prevalence of IPF is highly variable and ranges from 14-43 cases per 100,000 persons, while the incidence ranges from 7-16 cases per 100,000 persons.
- Internationally, prevalence and incidence rates are estimated at 10-20 and 7-10 cases per 100,000 persons, respectively.
- Patients with IPF are usually between 50 to 70 years of age at presentation, with approximately 75% of patients > 65 years of age.
- It is anticipated that the number of individuals diagnosed with IPF will continue to increase as a result of people living longer, improved clinical understanding and earlier and more accurate diagnosis.

Pirfenidone is Expected to Achieve Blockbuster Status Despite Modest Efficacy

- In 2008, pirfenidone was launched for the treatment of IPF in Japan and is currently approved in the European Union and Phase III in the US.
- Clinical studies have shown only modest efficacy data – CAPACITY 1 study failed to reach primary end-point; however, as a first-to-market therapy for IPF, pirfenidone has been forecasted to achieve blockbuster status.

Phase III Clinical Trial Results

- The approval of pirfenidone in Japan and its anticipated launch in the US and EU is a clear example of where a therapy showing only modest benefit for an indication with a huge unmet need (IPF) is expected to achieve significant revenues.

Source: EvaluatePharma, Oppenheimer & Co., 2010.
Bronchiectasis
The Global Prevalence of Bronchiectasis is Not Well Understood

- The epidemiology of bronchiectasis is not well documented due, in large part, to the fact that it is often misdiagnosed.
- The prevalence of bronchiectasis is thought to be much higher than the current number of patients seeking treatment; however, estimates of the undiagnosed patient populations are not known.
- Overall, there appears to be a global increasing trend of patients being diagnosed and treated for bronchiectasis. However, it is thought that this increase varies widely by country.
- The incidence of bronchiectasis increases with age and, for unknown reasons, it appears that women are affected more often than men.

Bronchiectasis is a Significant Cause of Morbidity and Mortality in Patients

- Chronic health issues are associated with bronchiectasis:
  - Cough and sputum production
  - Repeated respiratory infections
  - Atelectasis (collapsed lung)
  - Respiratory failure
  - Heart failure
  - Life expectancy is reduced in bronchiectasis patients and the 10-year mortality rate is estimated at 30%, roughly between asthma and COPD.

- Studies of long- and short-term outcomes in bronchiectasis patients are scarce and the prognosis of bronchiectasis is poorly understood, although it is clear that bronchiectasis is a significant cause of morbidity and mortality in patients.

- Currently, there are no approved therapies for bronchiectasis and treatment is limited to symptomatic management of exacerbations.

- ‘Off-label’ therapies are considered to be only moderately effective and do not modify the course of the disease.

Bronchitol – inhaled mannitol Pharmaxis

• Bronchitol (Pharmaxis) is currently in Phase III for bronchiectasis, is a near-term asset with transformative potential. There are no approved mucoactive agents available for bronchiectasis and, if approved, Bronchitol would become a first-in-class mucoactive agent and potentially standard of care.

• The lead indication for Bronchitol is cystic fibrosis, bronchiectasis being a fast-follower indication (currently Phase III, anticipated completion 2nd Phase III study August 2012, estimated NDA submission not before December 2012). Orphan designation has been granted for Cystic Fibrosis in US and EU, as well as FDA fast-track status for cystic fibrosis. Pharmaxis also intends to pursue COPD as an additional indication.

• Bronchitol has high visibility among physicians treating bronchiectatic patients, and is eagerly anticipated

1st Phase III trial
• 363 patient, controlled, double blind, randomised 12 week treatment (twice per day) + 12 month open label extension

Primary endpoints
• quality of life – validated Patient Reported Outcome
• mucus clearance – 24hr sputum volume

Primary Analysis
• quality of Life
  SGRQ, p<0.001 versus baseline
  SGRQ, p<0.05 versus placebo
• mucus clearance
  ↑30%, p<0.001 versus placebo
• antibiotic use reduction
  p<0.05 versus placebo
• adverse events (52 wks)
  cough 9%, sore throat 5%
  no SAE attributed to treatment

2nd Phase III trial
• 475 patient, controlled, double blind, randomised, 52 week treatment, 89 sites in US, Europe, South America, Australia
• 400mg twice a day

Primary endpoint
• Reduction in number of exacerbations

Secondary endpoints
• Exercise, mucus clearance, antibiotic use
• Quality of life

Status
• Special Protocol Assessment concluded with U.S. FDA
• Orphan Drug designation USA
• First patient enrolment October 2009
• Complete recruitment H1 2011
• Data 2012

Source: Pharmaxis company information
Conclusions

• So what is the relevance of these new approaches to companies currently outside the respiratory space?
  – The world-wide epidemiology and unmet needs deserve interest.
  – The highlighted programs mostly come from smaller biotech companies and are as yet unpartnered.
  – Pirfenidone in IPF, represents only a modest improvement in efficacy over off-label products, but with $1billion potential due to the high level of unmet need.
  – Others like IL-13/IL-4 for asthma show up our lack of understanding of the underlying biology and the lack of positive predictive animal models.
• Companies already vested in the space have challenges to overcome
  – The lack of understanding of the underlying biology means collaborations with academic institutions will be essential to allow a more targeted approach to disease management.
  – The FDA’s risk adverse approach for LABA’s may limit the ability of companies to optimize LABA containing combinations and open the door to alternate approaches.
  – The forthcoming patent expiry of major molecules means that more focus on identification of patient sub-groups will be needed to allow a specific niche to be exploited, avoiding head to head competition with generics that will benefit from extensive data on molecules.
Defined Health's Therapeutic Insight will be a featured track at these 2011 and 2012 EBD conferences: